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Highly Efficient Asymmetric Synthesis of Enantiopure Dihydro-1,2-oxazines: Dual-Organocatalyst-Promoted Asymmetric Cascade Reaction

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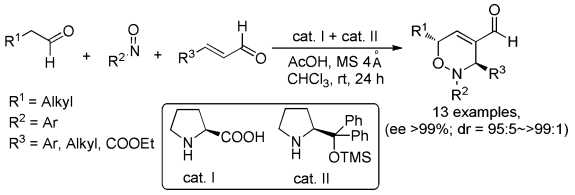
ABSTRACT



A one-pot dual-organocatalyst-promoted asymmetric α-aminoxylation/*aza*-Michael/aldol consendation cascade reaction is presented. The targeted optically active 1,2-oxazine derivatives are synthesized in moderate yields (up to 70%), excellent enantioselectivities (ee >99% in all cases), and excellent diastereoselectivities (dr up to >99:1) under mild conditions. To further elucidate the synthetic utility of the cascade products, cleavage of the N−O bond is demonstrated and an enantiopure *syn*-1,4-amino alcohol derivative is achieved in excellent yield.

Optically pure 1,2-oxazines have been used widely in the construction of biologically active compounds[1] and are valuable chiral building blocks.[2] Moreover, 1,2-oxazines also possess synthetic utility *via* reductive N−O bond cleavage to form highly functionalized 1,4-amino alcohols which can be found in a number of bioactive natural products. Recently, there has been great progress in the synthesis of 1,2-oxazines.[3] Whereas, there have been several methods for the synthesis of chiral tetrahydro-1,2-oxazines,[3l,n−q] only one general route was reported for the

(1) (a) Yu, Q.-S.; Zhu, X.; Holloway, H. W.; Whittaker, N . F.; Brossi, A.; Greig, N. H. *J. Med. Chem.* **2002**, *45*, 3684. (b) Judd, T. C.; Williams, R. M. *Angew. Chem.* **2002**, *114*, 4877. *Angew. Chem., Int. Ed.* **2002**, *41*, 4683. (c) Suzuki, M.; Kambe, J.; Tokuyama, H.; Fukuyama, T. *Angew. Chem.* **2002**, *114*, 4880. *Angew. Chem., Int. Ed.* **2002**, *41*, 4686. (d) Katoh, T.; Itoh, E.; Yoshino, T.; Terashima, S. *Tetrahedron* **1997**, *53*, 10229. (e) Terano, H.; Takase, S.; Hosoda, J.; Kohsaka, M. *J. Antibiot.* **1989**, *42*, 145. (f) Uchida, I.; Takase, S.; Kayakiri, H.; Kiyoto, S.; Hashimoto, M.; Tada, T.; Koda, S.; Morimoto, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4108. (g) Iwami, M.; Kiyoto, S.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1987**, *40*, 589. (h) Kiyoto, S.; Shibata, T.; Yamashita, M.; Komori, T.; Okuhara, M.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1987**, *40*, 594. (i) Shimomura, K.; Hirai, O.; Mizota, T.; Matsumoto, S.; Mori, J.; Shibayama, F.; Kikuchi, H. *J. Antibiot.* **1987**, *40*, 600. (j) Hirai, O.; Shimomura, K.; Mizota, T.; Matsumoto, S.; Mori, J.; Kikuchi, H. *J. Antibiot.* **1987**, *40*, 607. (k) Hori, Z.; Yamauchi, M.; Imanishi, T.; Parello, J.; Hanaoka, M.; Munavall, S. *Tetrahedron Lett.* **1972**, 1877.

(2) (a) Tsoungas, P. G. *Heterocycles* **2002**, *57*, 915. (b) Pulz, R.; Al-Harrasi, A.; Reissig, H.-U. *Org. Lett.* **2002**, *4*, 2353. (b) Tishkov, A. A.; Reissig, H.-U.; Loffe, S. L. *Synlett* **2002**, 863. (c) Buchholz, M.; Reissig, H.-U. *Eur. J. Org. Chem.* **2003**, 3524. (d) Al-Harrasi, A.; Reissig, H.-U. *Angew. Chem.* **2005**, *117*, 6383. *Angew. Chem., Int. Ed.* **2005**, *44*, 6227. For the total synthesis of (+)-phyllantidine from a cyclopropane, see: (e) Carson, C. A.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6560.

(3) For reviews on synthesis of 1,2-oxazines, see: (a) Gilchrist, T. L.; Wood, J. E. In *Comprehensive Heterocyclic Chemistry II*, Vol. 6; Elsevier: Oxford, U.K., 1996; pp 279−299 and 1177−1307. For the synthesis of 1,2-oxazines, see: (b) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317. (c) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137. (d) Ding, X.; Ukaji, Y.; Fujinami, S.; Inomata, K. *Chem. Lett.* **2003**, *32*, 582. (e) Koide, K.; Finkelstein, J. M.; Ball, Z.; Verdine, G. L. *J. Am. Chem. Soc.* **2001**, *123*, 398. (f) Young, I. S.; Williams, J. L.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 953. (g) Young, I. S.; Kerr, M. A. *Angew. Chem.* **2003**, *115*, 3131. *Angew. Chem., Int. Ed.* **2003**, *42*, 3023. (h) Kumarn, S.; Shaw, D. M.; Longbottom, D. A.; Ley, S. V. *Org. Lett.* **2005**, *7*, 4189. (i) Kumarn, S.; Shaw, D. M.; Ley, S. V. *Chem. Commun.* **2006**, 3211. (j) Yoon, S. C.; Kim, K.; Park, Y. J. *J. Org. Chem.* **2001**, *66*, 7334. (k) Pulz, R.; Cicchi, S.; Brandi, A.; Reissig, H.-U. *Eur. J. Org. Chem.* **2003**, 1153. (l) Yamamoto, Y.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5962. (m) Helms, M.; Schade, W.; Pulz, R.; Watanabe, T.; Al-Harrasi, A.; Fišera, L.; Hlobilová, I.; Zahn, G.; Reissig, H.-U. *Eur. J. Org. Chem.* **2005**, 1003. (n) Sibi, M. P.; Ma, Z. H.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 5764. (o) Momiyama, N.; Yamamoto, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 1190. (p) Lu, M.; Zhu, D.; Lu, Y.; Hou, Y.; Tan, B.; Zhong, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 10187. (q) Zhu, D.; Lu, M.; Chua, P. J.; Tan, B.; Wang, F.; Yang, X.; Zhong, G. *Org. Lett.* **2008**, *10*, 4585.

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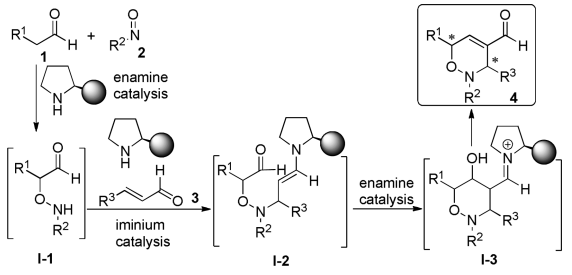
construction of dihydro-1,2-oxazines by Ley's group.[3h,i] It was rationlized that α-oxyamination of an enamine intermediate with nitrosobenzene[4] was followed by nucleophilic attack on a vinyl phosphonium salt, which would subsequently form a dihydro-1,2-oxazine through an intramolecular Wittig process. However, attempts to extend the reaction scope for this example are limited, and therefore the design and development of a practical, asymmetric synthetic cascade procedure to access enantiopure functionalized dihydro-1,2-oxazine from acyclic starting materials is still highly desirable.

Organocatalyzed cascade reactions which avoid time-consuming and costly protection/deprotection processes as well as the purification of intermediates represent a flourishing area in organic chemistry.[5] They can be applied to generate useful enantiomerically pure building blocks for the synthesis of biologically active natural products with excellent stereoselectivity and are environmentally friendly. Of all classes of structural organocatalysts, chiral secondary amines are probably the most commonly used to date and have shown excellent utility for a variety of enantioselective transformations. They activate various aldehydes by enamine formation (raising the HOMO) or α,β-unsaturated aldehydes by iminium-ion formation (lowering the LUMO).[6] This ability allows the catalyst to be ideally employed in cascade reactions, which proceed consecutively and under the same reaction conditions to construct complex frameworks from simple precursors.[7] Herein, we report our effort towards organocatalytic asymmetric assembly cascade reactions that provides an entry to enantioenriched 1,2-oxazines in high diastereo- and enantioselectivities.

We envisioned that α-oxyamination of the aldehyde **1** with nitroso compound **2** catalyzed by a proline-based secondary amine via an enamine process would yield **I-1**, which underwent *aza*-Michael addition *via* the same catalyst through an iminium process to provide the intermediate **I-2**, which then was subjected to an aldol condensation again *via* enamine catalysis induced by the same amine to finally afford trisubstituted functionalized dihydro-1,2-oxazine molecular **4** with two newly formed chiral centers (Scheme 1). However, three challenging issues affecting chemoselectivities need to be addressed: (1) α-aminoxylation intermediate **I-1** may itself oligomerize;[8] (2) **I-1** may further react with another molecule of the excess aldehyde **1** in the presence of proline by aldol reaction; (3) the *aza*-Michael addition step may be competing with the undesired Michael reaction between the aldehyde **1** and α,β-unsaturated aldehyde **3**. If these side effects were overcome and the desired transformations take place, we will be able to develop a general, facile, cascade approach for the synthesis of dihydro-1,2-oxazine. Herein, we report our efforts toward meeting these challenges.

Scheme 1. Proposed Organocatalytic Cascade Reaction for the Synthesis of Optically Dihydro-1,2-oxazines



Our preliminary experiments were initiated by using propanal **1a** and nitrosobenzene **2a** as model substrates, DMSO as the solvent, and L-proline as the catalyst in the first α-aminoxylation reaction.[7a] (*E*)-Hex-2-enal **3a** was selected as the model of α,β-unsaturated aldehyde in the second step and was added to the α-aminoxylation

(4) For aminoxylation of aldehydes, see: (a) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247. (b) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808. (c) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293. For ketones, see: (d) Bøgevig, A.; Sundén, H.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1109. (e) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 1112. For a review, see: (f) Yamamoto, H.; Momiyama, N. *Chem. Commun.* **2005**, 3514.

(5) For selected reviews, see: (a) Lehninger, A. L. *Principles of Biochemistry*; Worth, NY, 1993. (b) Katz, L. *Chem. Rev.* **1997**, *97*, 2557. (c) Koshla, C. *Chem. Rev.* **1997**, *97*, 2577. (d) Koshla, C.; Gokhale, R. S.; Jacobsen, J. R.; Cane, D. E. *Annu. Rev. Biochem.* **1999**, *68*, 219. (e) Mann, J. *Chemical Aspects of Biosynthesis*; Oxford Chemistry Primers, Oxford Univ. Press: Oxford, 1999. (f) Staunton, J.; Weissmann, K. J. *Nat. Prod. Rep.* **2001**, *18*, 380. (g) Enders, D.; Grondal, C.; Hüuttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (h) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037. (c) Alba, A.; Companyo, X.; Viviano, M.; Rios, R. *Curr. Org. Chem.* **2009**, *13*, 1432. (d) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167. (e) Mayano, A.; Rios, R. *Chem. Rev.* **2011**, *111*, 4703.

(6) For selected reviews, see: (a) Ahrendt, K. A.; Borth, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. (b) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458. (c) List, B. *Chem. Commun.* **2006**, 819and references therein. (d) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (e) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416. (f) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138. (g) MacMillan, D. W. C. *Nature* **2008**, *455*, 304.

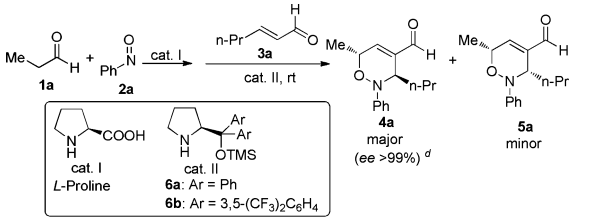
(7) For selected reviews and papers of amine-catalyzed cascade reactions, see: (a) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551. (b) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (c) Ramon, D. J.; Yus, M. *Angew. Chem.* **2005**, *117*, 1628. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (d) Guo, H.-C.; Ma, J.-A. *Angew. Chem.* **2006**, *118*, 362. *Angew. Chem., Int. Ed.* **2006**, *45*, 354. (e) Tietze, L. F.; Brasche, G.; Gerike, K. *Domino Reactions in Organic Chemistry*; Wiley-VCH: Weinheim, 2006. (f) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861. (g) Xie, H.; Zu, L.; Li, H.; Wang, J.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 10886. (h) Carlone, A.; Cabrera, S.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1101. (i) Zu, L.; Li, H.; Xie, H.; Wang, J.; Jiang, W.; Tang, Y.; Wang, W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3732. (j) Rueping, M.; Kuenkel, A.; Tato, F.; Bats, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3699. (k) Reyes, E.; Talavera, G.; Vicario, J. L.; Badía, D.; Carrillo, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 5701. (l) Galzerano, P.; Pesciaioli, F.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7892. (m) Michrowska, A.; List, B. *Nat. Chem.* **2009**, *1*, 225. (n) Zhang, X.; Zhang, S.; Wang, W. *Angew. Chem., Int. Ed.* **2010**, *49*, 1481. (o) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183. (p) Ling, J.-B.; Su, Y.; Zhu, H.-L.; Wang, G.-Y.; Xu, P.-F. *Org. Lett.* **2012**, *14*, 1090.

(8) Products of the α-aminoxylation of aldehydes aren't stable and can't be isolated in pure form because there are reactions that occurr between the aldehyde and the amino groups in the products (existing in the form of oligomers), therefore in situ reduction of the aldehydes to the corresponding alcohols is necessary to obtain pure products. For an example, see: Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Hibino, K.; Shoji, M. *J. Org. Chem.* **2004**, *69*, 5966.

reaction mixture until all the nitrosobenzene **2a** was consumed. Pleasingly, the cascade process proceeded smoothly to afford the desired product **4a** albeit with a complicated reaction mixture (Table 1, entry 1; 8% yield, dr = 52:48, ee >99%). Although proline has been reported to be an excellent enamine catalyst,[9] this amino acid is generally ineffective as an iminium catalyst[10] in the case of enals. Given these mutual reactivity profiles, we hypothesized that the combination of the readily available α, α-disubstituents prolinol trimethylsilyl ether catalyst **6a** or **6b** and proline should serve as a dual-catalyst system[11] that fully satisfied the chemoselective requirements for cycle-specific catalysis. As we predicted, the combination of catalyst **6a** and proline provided a better yield (20%) and dr (81:19), with no loss in enantioselectivity (ee >99%) (Table 1, entry 2). And the combination of the secondary amine with a strong electron-withdrawing substituent on the aryl rings of catalyst **6b** and proline gave a diminished result (Table 1, entry 3). To improve the yield, we resized the loading of the iminium catalyst **6a** to accelerate the *aza*-Michael reaction (Table 1, entry 4). Among the screened solvents ($CHCl_3$,[7b] CH_3CN,[7c] etc.), $CHCl_3$ proved to be the proper choice giving the best chemical yield and diastereoselectivity (Table 1, entries 5−6). We next examined the additive and ratio (both the ratio of catalysts and reagents) effect of this newly designed cascade transformation (Table 1, entries 7−10). Finally, the best conditions were established: First, α-aminoxylation was conducted at 0 °C, and then the *aza*-Michael/aldol condensation was conducted at room temperature, catalyzed by a dual-catalyst combination system [L-proline (10 mol %) and catalyst **6a** (30 mol %)], with AcOH (0.3 equiv) and 4 Å MS (100 mg) as additives and $CHCl_3$ as the solvent (Table 1, entry 10).

With the optimal reaction conditions in hand (Table 1, entry 10), the scope of this cascade reaction was investigated. A variety of aldehydes for the first α-aminoxylation were investigated. Butyraldehyde and 3-methylbutanal gave better results, with a 62% and 58% yield, dr = 96:4 and 97:3 respectively (Table 2, entries 2−3). A long chain aliphatic aldehyde, such as nonanal, is also a good substrate, providing the desired 1,2-oxazine product in good yield (Table 2, entry 4). Linear aliphatic aldehydes bearing some functional group such as OTs can be applied as substrates in the domino reaction as well (Table 2, entry 5). As the *para*-substituent of the phenyl ring of nitrosobenzene, either an electron-donating or -withdrawing group can be successfully employed to afford 1,2-oxazine derivatives in good yield (59−62%) with excellent diastereoselectivities (dr = 96:4) (Table 2, entries 6−8). Furthermore, this method was applicable to various α,β-unsaturated aldehydes. (*E*)-Pent-2-enal and (*E*)-dec-2-enal are suitable substrates (Table 2, entries 9−10). To our delight, with

Table 1. Optimization of the Reaction Conditions[a]



entry	sol.	cat. I	cat. II	*t* (h)	yield[b]	dr[c]
1	DMSO	30%	–	4	8%	52:48
2	DMSO/DCM	30%	**6a**/20%	4	20%	81:19
3	DMSO/DCM	30%	**6b**/20%	4	15%	57:43
4	DMSO/DCM	20%	**6a**/30%	12	24%	82:18
5	CH_3CN	20%	**6a**/30%	12	13%	84:16
6[e]	$CHCl_3$	20%	**6a**/30%	12	22%	92:8
7[e]	$CHCl_3$	10%	**6a**/20%	12	14%	94:6
8[e,f]	$CHCl_3$	10%	**6a**/20%	12	24%	96:4
9[e,g,h]	$CHCl_3$	10%	**6a**/20%	24	34%	96:4
10[e,g,i]	**$CHCl_3$**	**10%**	**6a**/**30%**	**24**	**44%**	**96:4**

[a] The reaction was performed using nitrosobenzene **2a** (0.5 mmol, 1 M), aldehyde **1a** (0.6 mmol), α,β-unsaturated aldehyde **3a** (1.0 mmol) and catalyst proline and **6** in indicated solvent. See Supporting Information for details. [b] Isolated yield of product **4a**. [c] Determined by ^{1}H NMR of the crude product. [d] For the determination of *ee*, see Supporting Information. [e] The first α-aminoxylation was conducted at 0 °C. [f] The reaction was performed using aldehyde **1a** (1.5 mmol). [g] AcOH (0.2 equiv) and 4 Å MS (100 mg) were added. [h] The reaction was performed using aldehyde **1a** (1.5 mmol) and α,β-unsaturated aldehyde **3a** (2.5 mmol) . [i] AcOH (0.3 equiv) and 4 Å MS (100 mg) were added.

(*E*)-ethyl 4-oxobut-2-enoate as the Michael acceptor and butyraldehyde or 3-methylbutanal as the α-aminoxylation aldehyde, the domino reaction proceeded smoothly, providing the desired 1,2-oxazine derivatives in good yields, 70% and 54%, respectively, with excellent diastereomeric ratios of greater than 99:1 (Table 2, entries 11−12). It is worth noting that aromatic α,β-unsaturated aldehydes can be employed in this reaction system, but the desired product coincidentally has the same polarity as the reagent α,β-unsaturated aldehydes leading to difficulty in the isolation of the desired 1,2-oxazine product by column chromatography, even with further reduction of the desired aldehyde to the corresponding alcohol. Only when utilizing the aromatic α,β-unsaturated aldehydes with a CF_3 group at the *para*-position on the phenyl ring, the product could be isolated in 37% yield still with excellent diastereoselectivity (Table 2, entry 13). It should be mentioned that, in all cases, the enantiomeric excess is more than 99%.

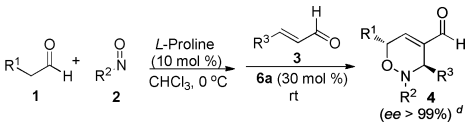
The absolute configuration of the cascade reaction product was identified unambiguously through X-ray

(9) (a) List, B. *Acc. Chem. Res.* **2004**, *37*, 548. (b) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.

(10) For a review of iminium catalysis, see: Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79.

(11) Simmons, B.; Walji, A. M.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 4349.

Table 2. Synthesis of Chiral Dihydro-1,2-oxazine[a]



entry	R^1, R^2, R^3	4	yield (%)[b]	dr[c]
1	R^1 = Me, R^2 = Ph, R^3 = *n*-Pr	**4a**	44	96:4
2	R^1 = Et, R^2 = Ph, R^3 = *n*-Pr	**4b**	62	96:4
3	R^1 = *i*-Pr, R^2 = Ph, R^3 = *n*-Pr	**4c**	58	97:3
4	R^1 = *n*-Hep, R^2 = Ph, R^3 = *n*-Pr	**4d**	51	95:5
5	R^1 = $TsOC_3H_6$, R^2 = Ph, R^3 = *n*-Pr	**4e**	33	98:2
6	R^1 = *i*-Pr, R^2 = 4-BrC_6H_4, R^3 = *n*-Pr,	**4f**	60	96:4
7	R^1 = *i*-Pr, R^2 = 4-$MeOC_6H_4$, R^3 = *n*-Pr	**4g**	59	>99:1
8	R^1 = *i*-Pr, R^2 = 4-ClC_6H_4, R^3 = *n*-Pr	**4h**	62	96:4
9	R^1 = *i*-Pr, R^2 = Ph, R^3 = Et	**4i**	35	96:4
10	R^1 = *i*-Pr, R^2 = Ph, R^3 = *n*-Hep	**4j**	50	95:5
11	R^1 = *i*-Pr, R^2 = Ph, R^3 = COOEt	**4k**	70	>99:1
12	R^1 = Et, R^2 = Ph, R^3 = COOEt	**4l**	54	>99:1
13	R^1 = *i*-Pr, R^2 = Ph, R^3 = 4-$CF_3C_6H_4$	**4m**	37	>99:1

[a] The reaction was performed using nitrosobenzene **2** (0.5 mmol, 1 M), aldehyde **1** (1.5 mmol), α,*β*-unsaturated aldehyde **3** (2.5 mmol), proline (10 mol %), catalyst **6a** (30 mol %), AcOH (0.3 equiv), and 4 Å MS (100 mg) in $CHCl_3$. See Supporting Information for details. [b] Yield of isolated product **4**. [c] Determined by ^1H NMR of the crude product. [d] For the determination of *ee*, see Supporting Information.

crystallographic analysis of (*R*)-*N*-*tert*-butylsulfinyl imine derivate **7a** derived from the corresponding adduct **4a** (Figure 1).

With optically pure 1,2-oxazines obtained, we next demonstrated the synthetic utility of the cascade products. Reduction of the 1,2-oxazine product **4a** with $NaBH_4$, followed by N−O bond hydrogenolysis by the Zn/HCl system, provides the corresponding valuable *syn*-1,4-amino alcohol derivative **8a** in 91% yield in two steps, without any loss of enantioselectivity (ee >99%). Because 1,4-amino alcohols are found extensively in nature and are a chiral building block, they are potentially useful for the preparation of conformationally restricted peptides and biologically

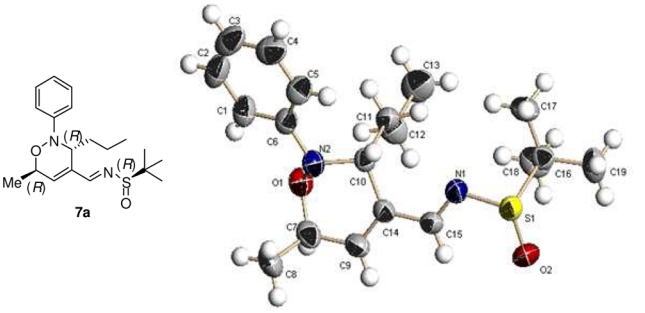
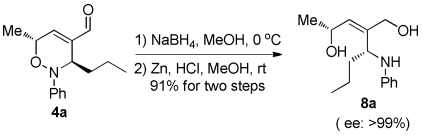


Figure 1. X-ray crystal structure of the enantiomerically pure (*R*)-*N*-*tert*-butylsulfinyl imine derivate.

Scheme 2. N−O Cleavage



active nonproteinogenic analogues. Thus, our route provides an easy access to a potentially diverse set of such compounds (Scheme 2).

In summary, we have developed a dual-organocatalyst-promoted asymmetric α-aminoxylation/*aza*-Michael/aldol consendation cascade reaction for the synthesis of chiral 1,2-oxazine derivates in good yield (up to 70%), with excellent enantio- (ee >99% in all cases) and diastereoselectivities (dr up to >99:1) under mild conditions. Notably, a multifunctional chiral *syn*-1,4-amino alcohol derivative could be prepared readily from the 1,2-oxazine derivates. We are currently investigating the catalytic mechanism of the cascade reaction and the application of this methodology to asymmetric syntheses of some natural and natural-like compounds and will be reporting the results in due course.

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Supporting Information Available. Experimental procedures and characterization data; copies of ^1H and ^{13}C NMR spectra and HPLC profiles. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.